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Findings of a hospital surveillance-based outcome evaluation study for *Clostridium difficile*-associated colitis

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Abstract

We completed a prospective study of 164 patients involved in a *Clostridium difficile* surveillance programme, evaluating a range of variables such as disease severity, treatment regimen and known clinical risk factors, for their effect on case lethality. The aim of this study was to determine if there are any additional clinical variables worth considering for inclusion in the therapeutic decision-making process. Beyond common risk factors, secondary immunodeficiencies such as diabetes mellitus, malignancy, autoimmune disease, immunosuppressive therapy and chronic hepatitis were assessed. Overall case lethality was 23%. There was a suggestion that regular proton pump inhibitor use in past medical history might be associated with greater lethality. Immunosuppressive therapy within 1 month before the onset of diarrhoea was associated with a significant four-fold lethality increase. This last finding may have the potential to further improve therapeutic judgement if used as an explicit component of a revised scoring system. In relation to *Clostridium difficile*-associated colitis, immunosuppressive therapy as a red flag entity, as described here, has not been previously published.

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Introduction

Clostridium difficile infection (CDI) remains one of the most challenging nosocomial infections worldwide. From 1986 to 2009 in Hungary, a total of four reported CDI epidemics took place (2001, 2003, 2004, 2009). In 2001, Urbán *et al.* [1] reported that out of 65 *C. difficile* isolates, the most common (39%) toxigenic type was PCR ribotype 087; there was no occurrence of the binary toxin. In 2003, the same team confirmed the presence of the binary toxin in two cases out of 112 *C. difficile* isolates; both were community-acquired infections [2]. An annual average of 43.8 CDI cases were reported in Hungary over the years 2004–08 [3]. During those 5 years, average morbidity was 0.4 per 100 000 population, with average lethality at 0.9%. In 2009 and 2010, average annual morbidity (2.1/100 000) and lethality (1.9%) figures rose to markedly higher levels. Terhes *et al.* [4] detected the first Hungarian case of *C. difficile* PCR ribotype 027 in a hospital setting in 2008. In 2010, nine hospital epidemics were registered, in three of which PCR ribotype 027 strains were confirmed [3]. Methodology guidelines in effect in Hungary as of 2011 classify CDI as a notifiable disease [3]. According to Hungary's National Nosocomial Surveillance System data, the number of sporadic cases in 2012 was 4506, as reported by 84 hospitals; the corresponding lethality figure was 22.3%. In 2011, the number of epidemics rose to 20, and in 2012 it was 21. However, no accurate national data on the PCR ribotype composition of the pathogenic strains are available [5]. In a recent Hungarian publication of ribotyping findings in 2010 and 2011, various *C. difficile* strains isolated from patients with diarrhoea and obtained from nationwide laboratory sources were found to be of the 027 ribotype in 30.4% of 601, and 50.2% of 699 cases, respectively; these results demonstrate an increasing tendency for the presence of ribotype 027 in the country [6].

The objective of our study was to analyse lethality risk factors in patients presenting with CDI over the course of an 18-month observation period, with the hypothesis that there might be extra clinical variables worth considering in therapeutic decision making.

Materials and Methods

Clostridium difficile follow-up service

Our 1173-bed hospital with an annual throughput of 864 inpatient person-years (2012 data) set up a *C. difficile* daily follow-up surveillance service, the only provider to do so in the country. From 1 January 2012 through to 1 July 2013, a total of 164 patients have been prospectively studied by the service. Patients were treated on the premises of the department where they acquired the infection. Most patients were treated by a general medical department; infections also occurred in departments of pulmonology, urology, infectious diseases, surgery, neurology, rheumatology and rehabilitation. The study was approved by the hospital's ethics committee.

Microbiological examination

Diarrhoeal faeces samples were tested using a rapid membrane enzyme immunoassay test (Techlab®, Wrexham, UK) for the simultaneous detection of *C. difficile* glutamate dehydrogenase antigen and toxins A and B. For glutamate-dehydrogenase-positive, toxin-negative results, the protocol prescribed a re-test of the faeces sample using a Wampole® (Alere, Waltham, MA, USA) immunoassay rapid test for toxin A and B detection. Cases that continued to be toxin negative upon the re-test were examined further by toxin A and B assay on isolated *C. difficile* (toxigenic culture). All samples that were positive on the toxin test were also cultured for the presence of *C. difficile*. None of the stools positive for *C. difficile* toxin contained any other enteric pathogens. The surveillance service was to be directly notified by the laboratory within 3–5 h of detecting antigen and toxin rapid test positivity in a patient suffering from diarrhoea.

Severity score system

Current protocols recommend, as a first choice, oral metronidazole in mild/moderate CDI and oral vancomycin in severe cases of CDI [7,8]. We assessed patients in terms of disease severity, treatment regimen and presence of clinical risk factors or immunosuppressed states, with the objective of evaluating the effects of these factors on case lethality.

Working as a locum specialist in Infectious Diseases for 3 months in 2011, the lead consultant of our surveillance service was a participating member of the *C. difficile* surveillance team of an NHS University Hospital in the UK. The Hungarian adaptation project of their methods served as the basis for our case severity scoring classification system, which was consistent with national CDI methodology guidelines issued in 2011.

The severity score was derived from a set of six parameters (Table 1). Severe radiological signs included intestinal distension in excess of 6 cm, ascites (unless attributable to a distinct cause other than the colitis), and pseudomembranous colitis. Cases were classified as mild to moderate when the total score was 0–2, and severe when it was 3–6; in consultations, our follow-up team recommended oral metronidazole treatment for non-severe, and oral vancomycin for severe cases.

Patients were score classified by the follow-up team on a single occasion immediately upon notification of the diagnosis of infection by the microbiological laboratory; therapeutic recommendations given to department medical personnel were based on the classification result. Mild and moderately severe cases were advised to be switched from first-choice metronidazole to vancomycin if the patient's condition and clinical symptoms either failed to improve within 3 days or deteriorated. Over the course of the observation period, neither stool transplantation nor fidaxomicin treatment was applied by our hospital.

Analysis

Unadjusted comparisons of patient subgroups were made using Fisher's exact tests. Multiple logistic regression analysis was used to estimate the effects of available clinical factors on case lethality in terms of OR. Explanatory variables included Charlson's index [9], a validated prognostic mortality indicator calculated from age group and comorbidity status. Age and sex were used as *a priori* adjustment variables. Factors observed to be irrelevant were eliminated to ensure model parsimony. Interactions between explanatory variables were explored and included if they were significant and clinically plausible.

TABLE 1. The severity score system applied in therapeutic decision making on patients with *Clostridium difficile*-associated colitis

Severity score points	
White blood cell count > 15 g/L	1 point
Albumin < 25 g/L	1 point
Acute rise of creatinine level	1 point
Stool count > 6/day	1 point
Body temperature > 38.3°C	1 point
Severe grade radiological signs	1 point
Total points maximum	6 points
Score evaluation	**Recommended therapy**
Non-severe case: 0–2 points	3 × 500 mg oral metronidazole
Severe case: 3–6 points	4 × 125 mg oral vancomycin

Sufficiency of model fit was checked using the Hosmer–Lemeshow goodness-of-fit test. The statistical package STATA (version 11; StataCorp, College Station, TX, USA) was used for data handling and analysis.

Results

Microbiological results

Antigen and toxin tests confirmed positivity in all 164 patients. In 161 patients, stool culture confirmed the presence of CDI, while culturing failed due to technical reasons in the remaining three cases. The 027 ribotype was confirmable through PCR in a single patient, who was successfully treated and recovered fully. Ribotyping, which current practice does not prescribe for sporadic cases, was not performed in other patients. Over the course of the observation period, no epidemic-level series of CDI emerged in our hospital.

Baseline characteristics of patients

A general description of the patient group is shown in Table 2. The male to female ratio (43.9–56.1%) was not significantly different across calendar years (p 0.873). As to risk factors, 130 patients (79.3%) were aged 65 years or older. Proton pump inhibitor (PPI) treatment within 1 month before symptom onset was found in the history of 96 subjects (58.5%), evaluated against a pooled reference group of patients who either had no history of acidity neutralizer treatment at all or had a history of histamine 2 (H2) receptor blocker use only. A history of antibiotic treatment before the infection was found in 93.9% (154 out of 164) of patients. Both these risk factors showed a decrease in frequency when comparing the two calendar years, to a non-significant extent (PPI from 63.3% to 51.5%; antibiotics from 96.9% to 89.4%).

TABLE 2. Patient characteristics assessed by gender, age, risk factors and incidence of relapses

	n (%) of patients 2012	2013	Total *n* (%)	p
All patients	98	66	164	
Age				
≤65 years	22 (22.5)	12 (18.2)	34 (20.7)	0.560
>65 years	76 (77.6)	54 (81.8)	130 (79.3)	
Gender				
Male	44 (44.9)	28 (42.4)	72 (43.9)	0.873
Female	54 (55.1)	38 (57.6)	92 (56.1)	
Risk factors				
Previous proton pump inhibitor	62 (63.3)	34 (51.5)	96 (58.5)	0.148
Previous antibiotic	95 (96.9)	59 (89.4)	154 (93.9)	0.091
Initial antibiotic treatment				
Metronidazole	44 (44.9)	26 (39.4)	70 (42.7)	0.140
Switched to vancomycin	29 (29.6)	29 (43.9)	58 (35.4)	
Vancomycin only	25 (25.5)	11 (16.7)	36 (22.0)	
Relapse	19 (19.4)	7 (10.6)	26 (15.9)	0.190

A total of 26 patients (15.9%) developed a relapse, with a lower observed incidence of such outcomes in 2013 compared with the previous year (10.6% versus 19.9%, p 0.190).

Immunosuppressed conditions

Secondary immunosuppressed state was defined as the presence of diabetes mellitus (50 patients, 31.45%), malignancy (32 patients, 20.13%), autoimmune disease (18 patients, 11%), immunosuppressive therapy in recent history (within a month) before onset of diarrhoea (13 patients, 8.18%), or chronic hepatitis (five patients, 3.14%). With the exception of immunosuppressive therapy, secondary immunosuppressive states listed above showed no significant association with lethality. A concise clinical description of patients receiving immunosuppressive therapy is shown in Table 3. The female to male ratio of these 13 patients was 10 : 3, and their mean age was 72.7 years. The most common primary disease of patients receiving immunosuppressive therapy was chronic obstructive pulmonary disease (seven patients, 54%). The treatment agent was a steroid in all cases, with the additional risk factor of previous antibiotic therapy being invariably present. No patients with primary immunodeficiency were observed.

Mortality and risk factors

The overall case lethality in our sample was 23% (38 patients out of 164). In 2012, 24 patients (24.5%) died, of whom four had developed a relapse; in 2013, 14 patients (21.2%) died, none of which were relapse cases. In all, 21 of the 38 fatalities underwent an autopsy, which confirmed pseudomembranous colitis in seven of those patients; in one patient, the presence of a causal relationship between CDI and the fatality could not be fully ascertained. In the 17 patients without autopsy, the treating physician declared a presumable causal association between CDI and the death judging by clinical progress.

We detected a significant interaction between treatment regimen and case severity. The treatment regimen effect estimates themselves were not significant, which is probably due to confounding by indication (Table 4). In the group of patients treated with metronidazole, cases classified as severe had close to 25 times the odds for death compared with non-severe cases (OR = 24.8, 95% CI 2.6–232.8; p 0.0049). This effect was diminished in the treatment switch group, and was barely present in patients treated with vancomycin as a first choice. The adjusted effect of PPI therapy, albeit not quite significant, suggested about double the odds for death relative to non-users or H2 blocker users (OR = 1.9, 95% CI 0.7–4.9; p 0.18). Prolonged immunosuppressive therapy was estimated to be associated with a lethality increase to more than four-fold (OR = 4.6, 95% CI 1.2–18; p 0.025). Charlson index, which was 6.8 points on average (SD 2.97) in the sample,

TABLE 3. Summary data of patients taking immunosuppressive therapy

No.	Age (years)	Gender	Immunosuppressive therapy	Indication of therapy	Days from treatment to diarrhoea	Comorbidity	Ab
1	70	M	Methylprednisolone	COPD	10	None	Y
2	85	F	Methylprednisolone	Acute bronchitis	3	DM, Hypertension	Y
3	78	F	Dexamethasone	Brain tumour	1	Hypertension	Y
4	53	F	Methylprednisolone	Breast cancer with lung and bone metastases	1	Cardiomyopathy	Y
5	73	F	Methylprednisolone	COPD	6	DM, Hypertension	Y
6	65	F	Methylprednisolone	COPD	25	Lung cancer with bone metastases	Y
7	80	F	Methylprednisolone	Acute bronchitis	25	Hypertension, Pacemaker implant	Y
8	69	M	Methylprednisolone	Klatskin tumour	>30 (long-term treatment)	None	Y
9	74	F	Methylprednisolone	COPD	29	DM, Pulmonary TB, Breast cancer	Y
10	81	F	Methylprednisolone	Pulmonary fibrosis	>30 (long-term treatment)	Hypertension, IHD	Y
11	90	F	Methylprednisolone	COPD	14	Hypertension, IHD	Y
12	53	M	Methylprednisolone	COPD	20	Cor pulmonale	Y
13	74	F	Methylprednisolone	COPD	20	DM, Pulmonary TB, Breast cancer	Y

Ab, antibiotics; COPD, chronic obstructive pulmonary disease; DM, diabetes mellitus; F, female; IHD, ischaemic heart disease; M, male; TB, tuberculosis; Y, yes.

TABLE 4. Multiple logistic regression estimates of the effects of various factors on the odds of lethality in *Clostridium difficile*-associated colitis

Factor	Contrast	Stratum	OR	95% CI	p
Therapy	M/V vs. M	Score = 0–2	1.876	0.589–5.969	0.2869
Therapy	M/V vs. M	Score = 3–6	0.123	0.012–1.306	0.0821
Therapy	V vs. M	Score = 0–2	2.040	0.537–7.756	0.2954
Therapy	V vs. M	Score = 3–6	0.103	0.007–1.449	0.0920
Score	3–6 vs. 0–2	Th = M	24.830	2.648–232.841	0.0049
Score	3–6 vs. 0–2	Th = M/V	1.625	0.389–6.792	0.5058
Score	3–6 vs. 0–2	Th = V	1.257	0.171–9.256	0.8221
Charlson index	+1 point	All patients	1.438	1.220–1.694	<0.0001
Age	+1 year	All patients	1.000	0.953–1.049	0.9958
Antacid therapy	PPI vs. none or H2 blocker only	All patients	1.916	0.738–4.975	0.1818
Prolonged immunosuppressive therapy	YES vs. no	All patients	4.659	1.205–18.021	0.0258
Sex	Male vs. female	All patients	1.463	0.588–3.641	0.4132

M, metronidazole; V, vancomycin; Th, therapy; PPI, proton pump inhibitor; H2, histamine 2 receptor.

produced a highly significant 44% increase in the odds of death with each one-point increase.

Discussion

International and local guidelines prescribe that metronidazole treatment is only to be chosen in the group of mild or moderately severe cases [3,7,8]. In cases where metronidazole therapy was started in the high (3–6) score category, the odds of mortality were close to 25 times greater than in the low-score group on the same treatment. The result indicates that the use of severity scoring facilitates decision making on initial therapy: for severe cases, i.e. those with score values 3–6, it gives a clear indication that they must be immediately started on vancomycin treatment. The reason why first treatment choices included metronidazole in the severe disease group nevertheless is because for some patients, therapy was started on a weekend or a holiday when the follow-up team was not available for immediate consultancy; also, department access to vancomycin could suffer a delay in some cases. A further subgroup of such cases came from occasional refusal by the treating physician to prescribe therapy in line with the surveillance service's recommendations. It is a limitation of our study that the first-choice therapy was out of line with case severity in a fifth of our patients for these reasons.

To our knowledge, there is nothing in the literature that establishes an association between immunosuppressive therapy and elevated lethality in CDI. Lübbert *et al.* compared 55 CDI patients receiving immunosuppressive therapy with 50 cases without such treatment in a retrospective, controlled, observational study [10]. Their regression analysis results suggested a role of immunosuppressive therapy as an independent risk factor for *C. difficile* colitis (OR = 2.75). In our analysis sample, patients receiving prolonged immunosuppressive therapy had a significant 4.7 times greater odds for fatality than those without such treatment. In conclusion, immunosuppressive therapy before the infection might be a red flag entity that, if included in the group of risk factors underlying the severity score, has the potential to further improve therapeutic judgement in these high-risk cases. Further research is required to assess independent predictive risk factors for their effect on case lethality in CDI, with

special emphasis on secondary immunosuppressed states; understanding these relationships better has the potential to improve choice algorithms for optimum treatment.

A meta-analysis published in 2012 by Janarthanan *et al.* demonstrated on observations from 300 000 patients that the proportion of cases of CDI among PPI users was as high as 65% [11]. No comparison with H2 blockers was undertaken in that analysis.

Another meta-analysis by Garey *et al.* investigated the risk factors for CDI relapse, including acidity neutralizers. The study confirmed the risk increase associated with concomitant use of acidity neutralizers and antibiotics in CDI; however, two of the three studies had no subgroup differentiation, therefore no stratified effect estimation for acidity neutralizer subgroups was possible [12]. A systematic multicentre meta-analysis by Tleyjeh *et al.* used the data of close to 202 000 patients to provide evidence for the risks associated with H2 blockers in CDI, primarily in a hospital setting, with concurrent antibiotic treatment [13]. The analysis did not address the effect of H2 blockers on CDI outcomes.

To date, there is only one population-based analysis to have studied the effects on outcomes of PPIs and H2 blockers in CDI [14]. In that retrospective study, the effect of the two medication types was evaluated in a pooled fashion; multiple regression analysis adjusted for age and comorbidities revealed no significant relationship between acidity neutralizer treatment and infection severity. A literature review and meta-analysis of data up to and including the year 2011 by Kwok *et al.* [15] revealed a possible association between PPI use and CDI. That communication was one of those that pointed out an additional risk increase when concomitant antibiotic treatment was applied. However, the analysis did not include a direct comparison of PPIs and H2 blockers in terms of their effects on CDI; instead, it only dealt with suggestions of side-effect control benefits associated with a switch from a PPI to a H2 blocker.

Our findings also suggest that the effects of multiple target proton pump inhibitors—as opposed to those of single-target H2 blockers—might represent an increased level of risk during CDI, and may change prognosis for the worse. If this can be confirmed by future studies, it might be wise to recommend general restrictions on continued PPI therapy in patients with CDI, except when thorough deliberation identifies such treatment to be indispensable.

Performance assessment studies on a number of CDI severity scoring systems are available in the literature [16,17]. Our local adaptation efforts of the system as used in the UK should be expanded to a nationwide level in Hungary to establish a practice of advanced and rapid professional therapeutic decision making in the management of patients with CDI.

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Contribution to Authorship

Istvan Varkonyi designed the surveillance system, interpreted the data, drafted and revised the manuscript critically and gave final approval of the submitted version. Eva Rakoczi designed and ran the surveillance system, interpreted the data, drafted and revised the manuscript critically and gave final approval of the submitted version. Olena Misak ran the surveillance system, interpreted the data, revised the manuscript critically and gave final approval of the submitted version. Erzsebet Komaromi acquired data, revised the manuscript critically and gave final approval of the submitted version. Laszlo Kardos statistically analysed the data, interpreted the findings, drafted and revised the manuscript critically and gave final approval of the submitted version. Zsolt Lampe supervised the design and operation of the surveillance system, interpreted the data, revised the manuscript critically and gave final approval of the submitted version. Zoltan Szilvassy provided a conceptual framework to the design and operation of the surveillance system, interpreted the data, revised the manuscript critically, and gave final approval of the submitted version.

Transparency Declaration

The authors declare no conflicts of interest.

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